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REVIEW ARTICLE

Proteoglycans in health and disease: structures and functions

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General composition and structure

Proteoglycans are macromolecules which consist of a protein backbone to which GAG chain(s) and *N*- and/or *O*-linked oligosaccharides are covalently attached (Fig. 1). The composition of GAG chains of PGs and their linkages to core proteins are described in Table 1. In the corneal stroma, KS is attached to protein by a linkage of the kind used to attach the complex-type and high-mannose oligosaccharides of glycoproteins and PGs to protein [118]. To the core proteins of all PGs are also bound *O*-linked oligosaccharides and/or complex-type *N*-linked oligosaccharides [81].

The core proteins of PGs have been the least well studied components of these molecules: this is discussed below. The complete core protein sequence has so far been established for only one PG [20]. In view of the considerable complexity of PG structure and composition, for us to organize a logical classification scheme for PGs we need to know not only the identities of the constituent GAGs but also, and primarily, the core-protein sequences. We will now discuss the different types of PGs and their known or suspected functions.

Chondroitin sulphate proteoglycans that aggregate with hyaluronic acid

The structures of some of these molecules are summarized in Table 2. The large aggregating PGs of cartilage represent the most studied of all PGs (Table 2). They are characterized by their very large size [83]. A HABR is located at the *N*-terminus [221] and constitutes about one-quarter to one-third of the total core protein [82]. This region can bind specifically to HA [77,82] with the formation of macromolecular aggregates [192]. These are organized between collagen fibrils with which the HA interacts [176]. Interaction of the PG with HA is stabilized by a link protein [13,76,230] which binds to the HABR in a molar ratio of 1:1 [177]. The binding of link protein to HABR and to HA leads to molecular shape changes in the link protein which can be detected immunologically [234]. Similar changes occur when HABR binds to HA [234]. Normally the HABR appears to be in the form of a well folded polypeptide chain with *N*-linked oligosaccharides [47,128] evenly distributed on the outside [168]. Little is known about the remainder of the core protein, but Perin *et al.* [167] have determined a 20-amino-acid *N*-terminal sequence (starting Met-Ile-Trp-His-) of a CNBr peptide from an aggregating cartilage PG, which is not present in the HABR.

Aggregating PGs of cartilage matrix contain 3–5 phosphoserine residues/mol of PG [3,170,206]. In addition, 2-phosphoxylose has been identified at 28 mol/mol of proteoglycan, or on one out of every three or four CS chains of the Swarm rat chondrosarcoma [153]. Phosphorylated xylose may act as a 'recognition signal' for the biosynthesis, packaging and/or translocation of PGs just as mannose 6-phosphate residues on *N*-linked oligosaccharides are involved in intracellular translocation and endocytosis [153].

Some molecules contain a region where KS chains are concentrated and which is adjacent to the HABR [88]. To the remainder of the core protein are attached most of the CS chains [79]. The very high charge density achieved by aggregated cartilage PGs permits these molecules to imbibe reversibly much water. They can occupy a solution volume of 30–50 times their dry weight [83,165] but in cartilage this swelling is limited by the network of collagen fibrils. The resulting swelling pressure endows cartilage with its compressive stiffness and its ability to sustain repeated loading during articulation [106,141].

When cartilage develops, the structures of these PGs change. The molecule that is synthesized in the fetus initially lacks KS. In man, this is added mainly after birth and increases in amount with age. This is accompanied by a shortening of CS chains, with an increase in the proportion of 6-sulphate, a reduced molecular size and an increase in the proportion of core protein [96,196,230]. The significance of these GAG changes remains to be established, particularly since skeletal KS is absent from mice and rats [243]. Recent studies have revealed that a second smaller KS-rich and uronic acid-deficient population appears after birth and increases in amount with age [16,92,237]. Ageing of human cartilage is accompanied by an accumulation of the HABR [197] and partially fragmented link proteins [139] In rabbits there is a decrease in link-stabilized PG aggregates with age [171]. These observations indicate that there is progressive degradation in cartilage with ageing, which would favour the development of osteoarthritic changes where a net loss of PG is associated with macroscopic degenerative changes [173]. In inflammatory arthritis, PGs can act as autoantigens and have been implicated in the immunopathology of the disease [37,68,74]

Cartilage PGs are concentrated in sites where matrix calcifies in endochondral bone formation [9,212] and hence may be involved, directly or indirectly, in conjunction with other matrix molecules, such as chondrocalcin [174], in the initiation of calcium phosphate deposition.

Abbreviations used: PG(s), proteoglycans(s); GAG(s), glycosaminoglycans; CS, chondroitin sulphate; DS, dermatan sulphate; HS, heparan sulphate; KS, keratan sulphate; HABR, hyaluronic acid binding region; HA, hyaluronic acid; PAPS, 3'-phosphoadenosine 5'-phosphosulphate.

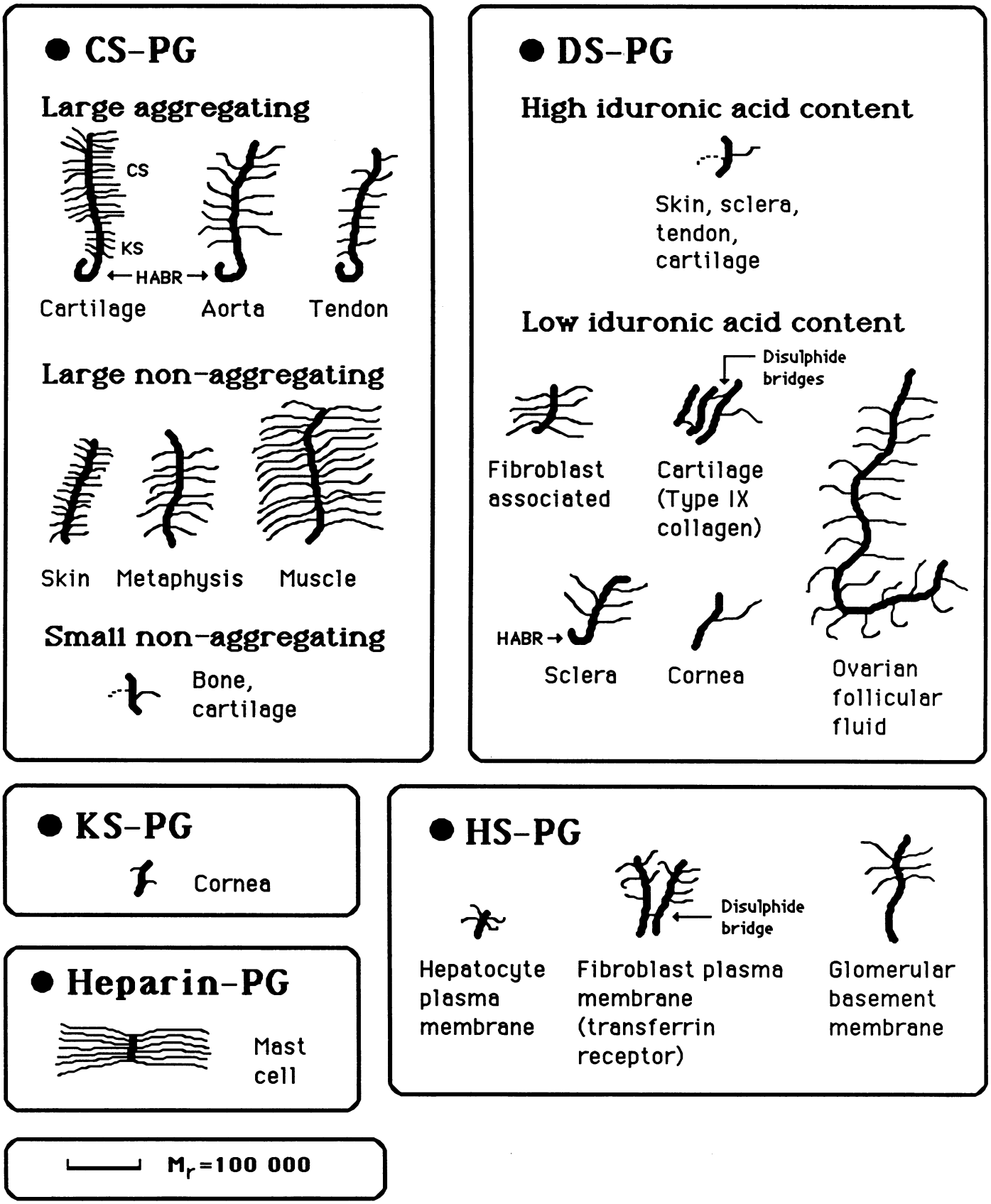

Fig. 1. Diagrammatic representation drawn to scale of some of the main PGs showing the different types and diversity of structure

Oligosaccharides are not shown. The core proteins are drawn thicker than the attached GAGs.

Table 1. Glycosaminoglycans of proteoglycans

Abbreviations: Ac, acetate; SA, sialic acid.

Glycosaminoglycan, repeating sequence and sulphation	Linkage to core protein
Chondroitin sulphate $\xrightarrow{\beta1,4}$GlcUA$\xrightarrow{\beta1,3}$GalNAc$\xrightarrow{\beta1,4}$GlcUA$\xrightarrow{\beta1,3}$ 4-or-6-SO_3^-	$\xrightarrow{\beta1,4}$GlcUA$\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,4}$Xyl$\xrightarrow{\beta1,0}$Ser
Dermatan sulphate $\xrightarrow{\beta1,4}$IdUA$\xrightarrow{\alpha1,3}$GalNAc$\xrightarrow{\beta1,4}$GlcUA$\xrightarrow{\beta1,3}$ $\pm$2-SO_3^- 4-or-6-SO_3^-	$\xrightarrow{\alpha1,3}$GalNAc$\xrightarrow{\beta1,4}$GlcUA$\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,4}$Xyl$\xrightarrow{\beta1,0}$Ser
Heparan sulphate and heparin 6-SO_3^- $\xrightarrow{\alpha1,4}$IdUA$\xrightarrow{\alpha1,4}$GlcN$\xrightarrow{\alpha1,4}$GlcUA$\xrightarrow{\beta1,4}$ 2-SO_3^- SO_3^- or Ac*	$\xrightarrow{\beta1,4}$GlcNAc$\xrightarrow{\alpha1,4}$GlcUA$\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,4}$Xyl$\xrightarrow{\beta1,0}$Ser
Keratan sulphate $\xrightarrow{\beta1,4}$GlcNac$\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,4}$GlcNAc 6-SO_3^-	**Cartilage** $\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,4}$GlcNAc$\xrightarrow{\beta1,6}$ Sa$\xrightarrow{\alpha2,3}$Gal$\xrightarrow{\beta1,3}$GalNAc$\xrightarrow{\alpha1,0}$Ser(Thr)
	Cornea $\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,4}$GlcNAc$\xrightarrow{\beta1,2}$Man$\xrightarrow{\alpha1,6}$ $\xrightarrow{\beta1,3}$Gal$\xrightarrow{\beta1,4}$GlcNAc$\xrightarrow{\beta1,2}$Man$\xrightarrow{\alpha1,3}$ Man$\xrightarrow{\beta1,4}$GlcNAc$\xrightarrow{\beta1,4}$GlcNAc$\xrightarrow{\beta1,N}$Asn $\alpha1,6$ Fuc

* Variable *N*-sulphation in heparan sulphate and extensive *N*-sulphation in heparin.

Table 2. Chondroitin sulphate proteoglycans

Many of the values shown are approximate. Abbreviation: ND, not determined.

		Glycosaminoglycans		Core protein			
Type	M_r	Chain number	M_r	M_r	Binds to HA	Tissue	References
Aggregating	2.5×10^6	100CS 30–60KS (often contains KS)	20000 6000	200000	+	Cartilage	79, 83, 88
	$(1–2) \times 10^6$	12	43000	200000	+	Aorta	4, 38, 152
	$(1–2) \times 10^6$	50	17000	> 200000	+	Tendon	2, 246
	ND	ND	ND	250000	+	Melanoma (cell surface)	25, 26
	150000	1–2	30000	70000	+	Brain	107
Large non-aggregating	1×10^6	50	20000	50000	–	Skin	45
	1×10^6	20	40000	200000	–	Metaphysis	55
	$> 2.5 \times 10^6$	ND	70000	ND	–	Skeletal muscle	34, 35
Small non-aggregating	70000	1–2	35000	35000	–	Bone	55, 65
	120000 76000	2–3	35000	42000	–	Cartilage	91

Aorta also contains large CS-PGs that aggregate with HA (Table 2). A link protein of size similar to the larger of the two major species found in cartilage is also present in aorta [67,175,245]. As in cartilage, aggregates of these PGs probably play a key role in maintaining shape and sustaining the repeated loading due to blood flow. A large aggregating CS-PG is also present in tendons (Table 2) and, like those PGs of cartilage and aorta, may perform an important role in dissipating load since it is more abundant in those parts of the tendon subjected to increased pressure [246].

Human melanoma cells have a large cell surface CS-PG that can bind to HA (Table 2). Monoclonal antibodies to this molecule can inhibit the growth of these tumour cells in soft agar [78] and block cell spreading on endothelial basement membranes [26].

A small aggregating CS-PG has been isolated from rat brain (Table 2). Like the glial cell and glioma PGs (see below), it also exhibits limited ability to aggregate with HA. Immunohistochemical studies have revealed that this molecule is present in the adult brain and spinal cord within neurons, astrocytes and the axoplasms of nerve fibres [5] where it may be responsible for maintaining shape, acting as an endoskeletal element. In contrast, in immature rats the molecule is almost exclusively extracellular and/or associated with plasma membranes [6].

Large non-aggregating chondroitin sulphate proteoglycans

Skin contains a large non-aggregating CS-PG (Table 2). Its amino acid composition is similar to that of the large aggregating cartilage PG but it lacks cystine and methionine. This is consistent with the lack of aggregation, since both of these amino acids are present in the HABR of the cartilage molecule [54,90] where cystine disulphide linkages are essential for the functional integrity of this region [79].

Another large PG is present in the soft tissue mesenchyme of the metaphysis lying between the trabeculae of forming bone (Table 2). It has a protein core similar in size to that of the aggregating cartilage PGs and cross-reacts with antibodies raised against these cartilage molecules.

Chick skeletal muscle synthesizes a CS-PG which has a larger hydrodynamic size and longer CS chains than PGs synthesized by chick chondrocytes (Table 2). This molecule is common early in myogenesis, and may be involved in the physical demarcation of developing muscles.

Small non-aggregating chondroitin sulphate proteoglycans

A major PG of bone (Table 2) is a molecule of small size and is similar to the small widely distributed DS-PG [55,65]. It is present in osteoblasts and bone, but not in cartilage. Antibodies to this molecule do not cross-react with the PG of skin or cornea [55] although others have reported immunological and peptide similarities with cornea, and the small PGs of sclera and tendon [89]. The major difference between these small PGs is probably whether DS or CS chains are synthesized.

Another similar small CS-PG is found in cartilage (Table 2). Immunochemical analysis and peptide mapping [89] have revealed that it is different from the small DS-PGs of cornea, sclera and tendon, but similar to a small PG isolated from aorta [200].

Dermatan sulphate proteoglycans

A number of PGs bearing DS (iduronic acid-containing) have been described. They vary in size and iduronic acid content. The major population is widely distributed and is a small PG (Table 3) with an M_r of 70000–100000 and a protein core which is probably of M_r 38000 [71]. The core protein can constitute from 30 to 60% of the total weight [41,44,191]. This molecule may have one [44,144]

Table 3. Dermatan sulphate proteoglycans

Many of the values shown are approximate. Abbreviation: ND, not determined.

	Glycosaminoglycans			Core protein			
M_r	Chain number	M_r	Iduronic acid content (%)	M_r	Binds to HA	Cell/tissue	Reference
70000–100000	1–2	15000–24000	35–85	40000	–	Skin	44, 71
						Sclera	41
						Cervix	239
						Cartilage	191
						Tendon	246
						Placenta	24
100000–150000	1	55000	10	40000	–	Cornea	11
1×10^6	ND	ND	25	400000	+	Fibroblast	31
160000–410000	ND	ND	20	100000	+	Sclera	41
2.5×10^6	50	40000	8	200000	+	Glial, glioma cells	149
70000–100000	1–2	15000–24000	23–36	40000	–	Cartilage (DS-PGI)	191
400000–800000	ND	40000	10	30000	–	Yolk sac tumour	155
500000	8	52000	7	43000	–	Embryonic cartilage	214
420000	1–2	40000	12	2×120000, 1×100000	–	Embryonic cartilage	150, 242
$(2–3) \times 10^6$	20	56000	9	500000	–	Follicular fluid	256

or possibly two DS chains which, within a tissue, can vary in iduronate content from 45 to 85% of the total hexuronate [211]. The length of this chain also shows tissue variations from M_r 15000 to 45000 [144,239]. The skin PG has three *O*-linked oligosaccharides [144] and one complex-type asparagine-linked oligosaccharide [213] per molecule. The amino acid composition of the core protein is quite different from that of the large aggregating cartilage PG. Partial sequencing of this molecule has revealed aspartic acid at the *N*-terminus [166]. The *N*-terminal sequence of the skin molecule is shared with that of the small cartilage DS-PG (L. C. Rosenberg, M. van der Rest & A. R. Poole, unpublished work) and is very similar to that of the human placental PG [24]. In both skin, cartilage and placenta, position 4 of the core protein is a serine residue and in each case there is probably either a DS chain or an *O*-linked oligosaccharide attached to it as shown for skin [166]. Immunological studies have revealed the relationship of the small cartilage molecule to that of sclera (L. Cöster, L. C. Rosenberg & A. R. Poole, unpublished work) and its unrelatedness to the large cartilage PG [191]. The small DS-PGs of sclera and tendon show immunological identity and have similar peptide patterns [89]. These identities and peptide maps are also shared with small PGs of bone and cornea [89] which contain CS with no iduronic acid [55,65]. Thus some PGs may have the same or very similar core proteins to which either CS or DS chains are attached, depending on whether glucuronic acid is epimerized to iduronic acid during synthesis.

Histochemical [208] and immunohistochemical [129] studies have indicated that this small DS-PG is bound to type I collagen at the d band in the gap zone [209]. Since the PG can inhibit fibrillogenesis of type I and type II collagens [247] it may play a key role in the regulation of collagen fibril assembly and in the biomechanical strength of collagen fibrils. In adult cartilage it is found mainly at the articular surface, where the collagen fibrils are thinner and arranged parallel with the surface, whereas during early development it is distributed throughout cartilage matrix [178].

DS chains with a high iduronic acid content, e.g. those found in the small DS-PG, can self-associate to form multimeric PG complexes [42,63]. This is a property of the arrangement of the glucuronic acid and iduronic acid components [59] and may indicate that DS-PGs on adjacent collagen fibrils can reversibly associate through their GAGs, assuming that they are bound to collagen by their core proteins as indicated [247]. Such DS chains also show high-affinity binding to low-density lipoproteins [61]. This may be of importance in atherosclerosis if these molecules are synthesized in excess in atheromas. Structural differences between DS-PGs from the arteries of pigeons with different susceptibilities to atherosclerosis have also been observed [198].

A small glucuronic acid-rich DS-PG is also present in the cornea (Table 3). The core protein is immunologically related to the small DS-PG of cartilage and sclera and has the same size (L. Cöster, L. C. Rosenberg & A. R. Poole, unpublished work). The molecular size of this corneal PG enables it to fit between the collagen fibrils, permitting corneal transparency [10]. In opaque corneal scars the interfibrillar spaces are abnormally large and contain an unusually large proteoglycan with glucuronic acid-rich chains of normal size; the KS-PG (described below) is absent [84]. When the scars heal, this PG returns to its normal size and the KS-PG reappears. Thus the PG may regulate collagen fibril spacing in the cornea, producing optical clarity.

Fibroblasts secrete the small DS-rich PG into culture medium but retain a larger molecule which is cell-associated and can bind to HA (Table 3). A large glucuronic acid-rich DS-PG is also found in the sclera (Table 3). Although it does not show evidence of aggregation with HA by gel chromatography, it does possess an immunoreactive HABR (L. Cöster, L. C. Rosenberg & A. R. Poole, unpublished work; [89]). Link protein is also present in sclera [175] and probably serves to stabilize aggregates of these PGs with HA. Like the aggregating PGs of cartilage, aorta and tendon, this molecule may play a key role in maintaining shape (of the eye) and sustaining intraocular pressure. Coffin–Lowry syndrome is a disorder marked by mental retardation, thick soft skin and skeletal abnormalities. Fibroblasts from these patients often exhibit abnormal synthesis of an increased proportion of the large glucuronic acid-rich DS-PG with an increased iduronic acid content, an increase in size of the smaller DS-PG and a reduction in the capacity of these molecules to be endocytosed [17]. This may reflect an abnormality in the core proteins, since endocytosis of these molecules is protein mediated [72].

Glial and glioma cells also synthesise very large glucuronic acid-rich PGs similar in size to the HA-aggregating cartilage PG, and which, like the cartilage molecules, also aggregate with HA (Table 3). This interaction can be stabilized by cartilage link protein [149], which has been detected immunologically in the central nervous system [175].

The other DS-PG of cartilage (DS-PGI) has an overall size and core protein similar to the smaller molecule (Table 3). Although it has a similar iduronic acid content to the smaller molecule, only the 'larger' species can self-associate, probably through its DS chains; it does not have an immunologically detectable HABR (L. Cöster, L. C. Rosenberg & A. R. Poole, unpublished work) and is immunologically unrelated to the other cartilage DS-PG called DS-PGII [191].

A large glucuronic acid-rich DS-PG has been isolated from the ascites fluid of a rat yolk sac tumour (Table 3). The PG is present on the cell surface [155] and can bind by its core protein [155] to type I collagen and fibronectin [23]. Bowdon *et al.* [20] identified the complete sequence of the cDNA for this PG. The 104-amino-acid protein sequence is composed of three regions, one of which is a central 49-amino-acid region composed of alternating serine and glycine residues. This region is where the GAG is bound. It is flanked by the 14-amino-acid *N*-terminal region [155] and, on the other side, by a 41-amino-acid *C*-terminal region. A single mRNA of 1300 nucleotides was observed. The structure of the serine/glycine region closely parallels that predicted by Robinson *et al.* [184] for the heparin-attachment region of a rat heparin PG, indicating that this repeat may be a feature of at least a subset of PGs.

A small DS-PG of developing chick cartilage has a core protein similar to the small skin, scleral and cartilage species, but contains little iduronate (Table 3). Another cartilage PG, originally called PG-Lt [150], with a low iduronic acid content, has now also been identified as type IX collagen (Table 3). It contains three collagen α chains linked by disulphide bridges; to one chain is attached one or two DS chains [150,241,242] (Fig. 1).

Ovarian follicular fluid contains a very large PG (Table 3). The DS chains are long. In addition, the molecule contains about 350 *N*-and *O*-linked oligosaccharide chains [256]. It must endow follicular fluid with high viscosity and maintain follicular shape by its hydration properties. Since it is readily degraded by plasmin [256] the activity of plasminogen activator, which increases at the time of follicular rupture [224], would favour escape of the oocyte as a result of degradation of this molecule. Ovarian granulosa cells also produce a smaller molecule of size similar to the larger scleral species [254]. Arterial tissue contains a molecule with a size and DS content similar to the large DS molecule isolated from cartilage [202]. Thus there is a considerable diversity of structure and composition in these PGs, the functions of which generally remain to be established.

Corneal keratan sulphate proteoglycan

In addition to the large aggregating KS-containing cartilage PGs the cornea also contains KS bound to a protein core of M_r about 30000–40000; one or two KS chains of M_r 7000 are *N*-linked to asparagine (Table 1). This GAG linkage is not known in other PGs. *N*-Linked oligosaccharides are also present [12,85]. With the glucuronic acid-rich DS-PG, these molecules play a critical interfibrillar role in determining the optical clarity of the cornea [10]. Macular corneal dystrophy is a human genetic disorder characterized by corneal opacity due to a defect in the synthesis of corneal KS-PG [86], namely a lack of sulphation of the keratan chain [145]. The glucuronic acid-rich DS-PG which is also synthesized by macular stromocytes is larger, more sulphated and contains fewer *N*-linked oligosaccharides than its normal counterpart. It has been suggested that the oversulphation is a compensatory response to the sulphation deficiency in the KS-PG [145].

Heparan sulphate proteoglycans

A review of the structure and function of heparan sulphate PGs by J. T. Gallagher, M. Lyon & W. P. Steward will appear in Biochem. J. **236**, 313–325 (1986).

Cell surfaces. HS-PGs are common cell surface constituents of most if not all cells. A HS-PG is present on rat liver cells (Table 4) which is intercalated in the lipid bilayer of the plasma membrane [115]; it is present on hepatocytes but restricted to the sinusoidal domain of the plasma membranes [223].

The HS-PG of fibroblasts (Table 4) has two core proteins linked by disulphide bridges. To each polypeptide are attached HS chains together with an unknown number of oligosaccharides. Each core protein probably consists of an HS-containing region of M_r 70000, an oligosaccharide-containing region and a non-glycosylated region. The whole molecule has an M_r of 300000–400000 [32,43]. Trypsin treatment of this molecule or reduction and alkylation produces a component of M_r 140000 of a size comparable with that found in fibroblast culture media [32] which may thus be a proteolytic cleavage product of the cell-associated molecule. Fransson *et al.* [58] found that this PG and the transferrin receptor are identical or very similar. They suggested that the function of this receptor may be regulated by an endo-β-glucuronidase working at the cell surface, since rapidly growing cells that express more functional transferrin receptor at their cell surface [147] release HS from the cell during active growth in G_2 [119].

The attachment and spreading of cells to their substrata in both stationary and locomoting cells is probably mediated by cell surface HS-PG. Focal cell footpad adhesion sites are enriched in HS-PG [121,190,251]. Binding is mediated by the HS chains [124] and involves attachment to fibronectin or platelet factor 4. Cell-mediated cleavage of the HS chains may permit cells to attach and detach [122]. Fibronectin has a specific binding site for HS [123,253]. HS isolated from the surfaces of non-adherent mouse myeloma cells does not bind to plasma fibronection but binds partially to type I collagen [220]. In contrast, HS isolated from two adherent mouse cell lines binds to fibronectin and type I collagen. Cell binding follows the same specificities as those observed for isolated molecules. A mammary epithelial cell HS-PG which is deposited on the basal surfaces of these cells also binds tightly to type I collagen but only in its intact state [116]. Since type I collagen fibrils cause these cells to accumulate a basement-membrane-like layer, this interaction may be important in the creation of basement membranes.

HS has the capacity to self-associate with HS of similar structure in a specific manner [56,57,62]. This is dependent upon co-operative interactions between contact

Table 4. Heparan sulphate and heparin proteoglycans

Many of the values shown are approximate. Abbreviation: ND, not determined.

Type	M_r	Glycosaminoglycans		Core protein M_r	Cell/tissue	Reference
		Chain number	M_r			
Cell surface HS	75000	4	14000	30000	Liver cell surface	157
	350000	4–6 per polypeptide	20000	2 × 90000	Fibroblast cell surface	32,43
	100000–200000	ND	ND	105000	Synaptic vesicles	30
Basement membrane HS	130000–250000	4–5	25000	90000–170000	Glomerulus	99, 101, 102, 164
	> 750000	6–12	70000	350000	Engelbreth–Holm–Swarm sarcoma	87
	400000	10	25000	150000	PYS-2 terato-carcinoma cells	158
Heparin	1×10^6	9–12	50000–100000	20000	Mast cell	18, 94, 184, 257

zones which probably correspond to the *N*-sulphated segments containing both iduronate and glucuronate. Given differences in HS composition and structure from one cell type to another [49], this self-association may play a major role in cell–cell recognitions [49] and interactions of cell surface PGs with those of HS-PGs in basement membranes. In quiescent cells HS-PG is retained on the cell surface, but during growth it is lost and that which remains has a reduced self-affinity [60]. This would fit with a loss of cell–cell interaction which is required for cells to divide and multiply. In tumour cells, which are usually rapidly growing, this PG is also deficient at the cell surface [60] and the HS shows either no self-association [64] or lacks affinity for one particular subtype, as is observed in normal cells [60]. Together these observations point to the importance of these PGs in cell–cell and cell–environmental interactions, and that their organization is changed and fundamentally disturbed in tumour cells resulting in changes in cellular behaviour.

PGs of this type may play an integral structural role in neurotransmission. A uronic acid- and glucosamine-rich molecule is a major component of synaptic vesicles (Table 4) and is probably also present on the outside of the intact nerve terminal. The HS of such a PG is probably responsible for the anchorage of the collagen-tailed acetylcholinesterase to the synaptic basal lamina [21].

Basement membranes. In addition to type IV collagen and laminin, basement membranes contain a HS-PG which appears to be distinct from that at the cell surface (Table 4). The charge-selectiveness of glomerular filtration owes its special properties to the HS of this molecule [99,102]. A deficiency of this PG would be expected to lead to enhanced glomerular permeability as is observed in a diabetic nephropathy [33], and in congenital nephrotic syndrome HS-PG is in fact reduced in concentration [244]. In streptozotocin-induced diabetes, the synthesis of this molecule is reduced [100] but can be restored to normal by insulin sufficient to maintain plasma glucose at normal levels [189].

The molecule isolated from glomeruli (Table 4) has GAG chains that are clustered in a very limited segment of the polypeptide. *N*-Sulphation is uneven and preferentially localized in those parts most remote from the core protein. *O*- and *N*-linked oligosaccharides are present [164]. Self-association of HS chains (see above) may play a role in the macromolecular organization of the molecule in the basement membrane. The core protein, which constitutes 70% by weight of the molecule, is unusual in that it has a remarkably large number of half-cystine residues (61/1000) [164]. These PGs of glomerular basement membranes are smaller than the larger HS-PGs isolated from the mouse Engelbreth–Holm–Swarm sarcoma and the PYS-2 mouse teratocarcinoma-derived cell line (Table 4). These large sizes may represent an abnormal processing in these tumours.

Heparin proteoglycan

The rat mast cell PG (Table 4) has a small core protein with a repeating sequence of serine and glycine residues [184,257]. To about two of every three serine residues are attached heparin chains of M_r 80000–100000 [184] which can be cleaved by a mastocytomal endoglycosidase to yield partially depolymerized products of M_r 7000–25000, similar to those of commercial heparin. The endoglucuronidase which is capable of degrading heparin [249] may participate in cleavage of heparin when it is secreted from mast cells, yielding smaller biologically active products. Studies of the mouse mastocytoma have not detected a large heparin PG, almost certainly because it contains a heparin-degrading glycosidase [154]. Antithrombin is a proteinase inhibitor that neutralizes the activities of serine proteinases of the coagulation cascade, including thrombin, by forming a 1:1 stoichiometric complex. Heparin binds to lysyl residues on antithrombin and accelerates complex formation by about 1000-fold [194]; activity resides in specific heparin tetrasaccharide [193] and decasaccharide [125] sequences. Heparin may also modulate the alternative complement pathway by regulating formation of C3 convertase [105]. It can also suppress the proliferation of vascular smooth muscle cells *in vivo* [39]. It rapidly inhibits DNA and RNA synthesis but has no effect on the overall rate of protein synthesis [36] although it produces qualitative changes in the biosynthesis of both non-collagenous and collagenous proteins [40,130,131].

Biosynthesis: normal and pathological

Our knowledge of the biosynthesis of these molecules has been derived primarily from studies of cartilage PGs. A functional HABR and core protein is assembled in the rough endoplasmic reticulum [53] where in tumour chondrocytes it remains for 70–90% of its intracellular half-life; in the Swarm rat chondrosarcoma it consists of one major species with an apparent M_r of 370000 [113] of a size similar to that found in cell extracts [148, 162] and produced by cell-free translation of chick [239] and bovine [236] chondrocyte RNA. Physicochemical estimates of the size of the core protein for completed PGs have produced values for M_r of 200000–230000 [83,165,182]. Nanomelia in chicks [8] and the mouse mutation known as cartilage-matrix deficiency (*cmd/cmd*) [108] are both lethal and result from a lack of synthesis of the core protein of aggregating cartilage PGs. This produces skeletal deformities in which the matrix is considerably reduced in volume due to the absence of PG.

During normal synthesis, the core protein enters the endoplasmic reticulum and assembly of *N*-linked high-mannose-containing oligosaccharides commences ([112]; Table 2) through a dolichol diphosphate intermediate oligosaccharide which is then transferred intact via a *N*-glycosidic bond to asparagine on the core protein [225,248]. Conversion of high-mannose oligosaccharide to the sialic acid-containing complex-type oligosaccharide occurs later in the Golgi [50].

In tumour chondrocytes, the assembly of CS chains (half-life of 10 min) and *O*-linked oligosaccharides (half-life of 15 min), and probably KS, also take place in the Golgi apparatus [112,233]. KS chains may be elongated on a 'primer' *O*-linked oligosaccharide [80]. The initiation and completion of CS occurs rapidly within the Golgi after a comparatively long delay from synthesis of the core protein (half-life for core protein is 90 min) [53,109,136]. Since, however, the addition of xylose to core protein appears to precede that of galactose by about 5 min [112], xylosylation of core protein may occur before the Golgi. This is also indicated by the demonstration of xylosyltransferase in the endoplasmic reticulum [93].

Chain synthesis of GAGs results from the successive addition of single sugars from uridine nucleotide sugar precursors by the action of glycosyltransferases

[187,219,233]. The key intermediates are UDP-glucose and UDP-*N*-acetylglucosamine. the former can be oxidized to form UDP-glucuronic acid which can then be decarboxylated to form UDP-xylose. Both UDP-glucose and UDP-*N*-acetylglucosamine can undergo epimerization at the C-4 position to form UDP-galactose and UDP-*N*-acetylgalactosamine, respectively [218]. The termination of chain elongation in CS may be achieved by 4-sulphation of terminal hexosamine residues since this, together with selective 4- and 6-sulphation, is a feature of newly synthesized CS chains [161]; CS chains ending in *N*-acetylgalactosamine 4-sulphate are unable to accept a glucuronic acid [186,217,233].

When PG synthesis is inhibited with cycloheximide [136] or puromycin [28], chain length increases. In contrast, β-xyloside, which can act as an alternative artificial acceptor for chain assembly, stimulates CS synthesis but shortens chain length [204,205] even on a core protein where there is reduced chain initiation [137,205]. These observations indicate that the glycosylaton of core protein is governed by the concentration of core protein present at any one time in the Golgi, given a localized and highly organized transferase assembly mechanism. Moreover, the increase in alternative free xylose acceptors for chain initiation would be expected to lead to a reduction in chain initiation on PG core and a shortening of chain length. Likewise, fewer acceptor sites with reduced core protein synthesis would be expected to lead to chain elongation, as has been observed. Thus, if the translocation of the core protein were accelerated or decelerated, chain assembly may be shortened or lengthened, respectively. Chain length can vary significantly. The polydispersity in size of aggregating cartilage PGs is due to variations in assembled CS chain length [54].

Radioautography has clearly shown that the sulphation of GAGs occurs in the Golgi apparatus [73,169]. Sulphation of GAGs is mediated by PAPS [183] from which sulphate is transferred by different sulphotransferases to the specific sites on the GAG. Sulphation probably takes place simultaneously with chain polymerization [48]. In heparin, and to a lesser degree in HS, there is an *N*-sulphation, in contrast with the *N*-acetylation found in other GAGs. Here sulphation proceeds through the formation of a GAG containing *N*-acetylglucosamine [215] which is then deacetylated with the replacement of the acetyl group by sulphate [126,216]. After sulphation has occurred, epimerization of D-glucuronosyl takes place to produce L-iduronic acid in DS, heparin and HS [95,133]. These biosynthetic events are summarized in Fig. 2.

Brachymorphic mice suffer severe skeletal abnormalities as a result of a reduction in cartilage PG sulphate content [160]. This undersulphation is due to the limited synthesis of the sulphate donor, PAPS, as a result of defects in adenosine 5′-phosphosulphate kinase and ATP sulphurylase [207,228]. Since cartilage, liver and kidney are affected but skin and brain are unaffected there may be tissue-specific forms of the defective enzymes [229]. A related human condition is a form of spondyloepiphyseal dysplasia where there is evidence for undersulphation of CS and a deficiency of the sulphotransferase which donates sulphate from PAPS [140].

The synthesis of oligosaccharides and GAGs in the Golgi appears to be a comparatively rapid affair in that, together with secretion, it probably occupies only 10–20% of the total time taken from core protein synthesis to secretion of the completed PG, which may be as long as 100 min in the rat chondrosarcoma. Secretion time from the Golgi may take as little as 5 min [112]. This rather slow synthesis of the large and complex cartilage PG is not shared by the much smaller and simpler DS-PGs which have a half life of only 12 min from core protein assembly to complete assembly of the molecule [71].

Cartilage PGs, which aggregate with HA, are secreted as a link protein–PG monomer complex which then proceeds to aggregate irreversibly with HA to form a stable complex [110,111]. A delay in aggregation with HA has been detected in adult human cartilage [15,151] and can be prevented by the addition of link protein [135]. Thus link protein may play an important regulatory role in aggregate formation as well as in its stability, although the synthesis of link protein can occur independently from that of PG monomer [134,172].

Regulation of biosynthesis

The most important molecules required for PG synthesis in chondrocytes from tumours, embryonic cartilage and young animals are probably insulin [180,222] and insulin-like growth factor I which is more active than somatomedin A and insulin-like growth factor II [98]. The stimulatory effect of ascorbic acid on PG synthesis has been well established [180,203]. Platelet-derived growth factor [180] and pituitary-derived fibroblast growth factor [103] both stimulate synthesis. Whether these effects are maintained in the adult remains to be seen. Although high doses of glucocorticoids have a degradative effect on cartilage matrix, recent studies have revealed that low doses of both hydrocortisone and dexamethasone can stimulate synthesis, particularly in the case of the large cartilage PGs where a 33-fold stimulation was observed [104]. In contrast, some prostaglandins inhibit the synthesis of cartilage PGs, in particular prostaglandins E_1, E_2, A_1 and B_1 [51,127,132,138].

Granulosa cells isolated from immature female rats injected with gonadotrophin synthesize two recognizable populations of PGs, one large and one small [255]. Follicle-stimulating hormone, luteinizing hormone, chorionic gonadotrophin and testosterone all stimulate synthesis, but only of the smaller PG population. This selective effect on the synthesis of one population of PGs is paralleled by the observations that glucocorticoids have a more stimulatory effect on the synthesis of the larger PGs of chondrocytes [104]. In contrast with chondrocytes, prostaglandins E_1 and E_2 can stimulate synthesis in granulosa cells [255]. Thus the synthesis of different proteoglycans within cells and in different cell types is clearly individually regulated.

Degradation of proteoglycans: normal and pathological

This is a normal physiological event which involves a regular turnover of extracellular PGs [218]. All PGs containing CS, DS, HS and KS are probably initially degraded in extracellular sites by cleavage of the core protein: there is no evidence for GAG cleavage in extracellular sites [52,181,238] except for HS (see below). These degradation products may either be locally endocytosed and digested or pass in the lymph and blood to the liver when endocytosis occurs.

Studies of aggregating cartilage PG monomers have

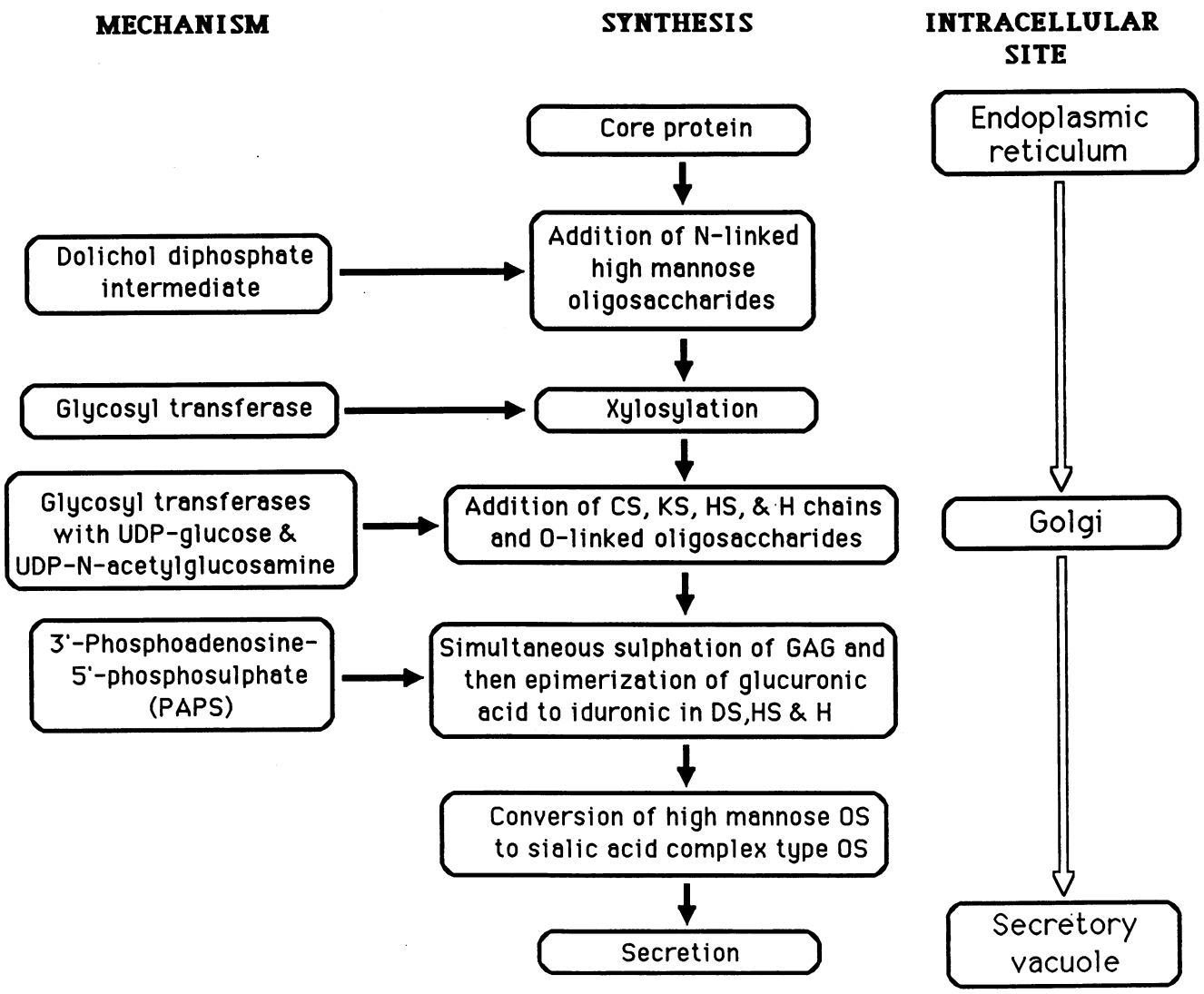

Fig. 2. Biosynthesis of proteoglycans

Additional abbreviations: H, heparin; OS, oligosaccharide.

revealed that the site of cleavage on the core protein depends upon the proteinase [195]. When PGs are present in aggregate form with link protein, the HABR is protected whilst the remainder of the molecule is cleaved [29,66,90]. A single cleavage close to the HABR with the release from the matrix of a non-aggregating monomer of slightly reduced size appears to take place when cartilage PGs are degraded [75,201,238] without any evidence of GAG cleavage [238, 250]. In spite of many years of research, the identity of the proteinase(s) producing this cleavage remains to be elucidated, although the neutral metalloproteoglycanase [66] is a strong candidate [27].

HS can be cleaved in extracellular sites by heparanases (heparitinases) produced by platelets [159,249,252] and activated T lymphocytes [146]. These enzymes, which may all be endoglucuronidases like the platelet enzyme [159], probably play a very important role in the initiation of extracellular cleavage of HS. Degradation of HS is no doubt very important since this GAG is bound both to fibronectin [199] and to types I, III and V collagens [117] in the extracellular matrix. The binding of HS to type I collagen considerably reduces degradation of the PG in culture [46]; cleavage of HS permits endocytosis and further intracellular digestion of this molecule. The entry of extracellularly cleaved and mobilized PGs into the cell is probably regulated by specific receptors. The endocytosis of the small DS-PG is protein-core-mediated [72].

The intracellular digestion of endocytosed PGs is completed within the lysosome. Core protein digestion would proceed by the action of the aspartate proteinase cathepsin D and the cysteine proteinases cathepsin H, B and L. The digestion of intact GAGs is initiated by endohexosaminidase or endoglucuronidase activity [1,69,231]. Oligosaccharides are then cleaved sequentially by exoglycosidases and sulphatases working from the non-reducing terminus. The digestion of CS-oligosaccharides in which there is a *N*-acetylgalactosamine residue at the non-reducing terminus is initiated by sulphatase followed by β-*N*-acetylgalactosaminidase and then β-glucuronidase, producing inorganic sulphate and monosaccharides [97].

The degradation of DS probably initially involves the action of an endohexosaminidase. Continuing stepwise

degradation from the non-reducing terminus would require the action of β-glucuronidase, *N*-acetylgalactosamine 4- or 6-sulphate sulphatase, iduronate 2-sulphate sulphatase, β-*N*-acetylhexosaminidase and α-L-iduronidase [185].

KS is degraded by the sequential action of the exoglycosidases β-D-acetylhexosaminidase and β-D-galactosidase. The *N*-acetylgalactosamine 6-sulphate sulphatase and galactose 6-sulphate sulphatase activites are in fact part of the same molecule and only the latter activity seems to be active in fibroblasts [70].

Heparin can be degraded in liver to large fragments of M_r about 4000 [7]. Mouse mastocytoma cells contain an endoglucuronidase which initially cleaves heparin to large oligosacharides [154]. This would be followed by the stepwise action of a series of enzymes removing sulphate, iduronic acid, acetylating the amino group of the non-reducing terminal glucosamine, then removing *N*-acetylglucosamine and glucuronic acid [185]. HS is degraded similarly [185] following endoglucuronidase activity [114,156].

Much of our knowledge of the degradation of GAGs has come from studies of patients with genetic abnormalities resulting in a deficiency or absence of a specific enzyme involved in GAG degradation. If an enzyme is absent a block occurs in the degradation and the GAG accumulates within the lysosome. These patients are said to suffer a 'mucopolysaccharidosis' or a 'storage disease'. These and GAG degradation have been elegantly reviewed recently by Kresse *et al.* [120] and the reader is referred to that review for a detailed survey of the deficiencies.

Excessive degradation of cartilage PGs and eventually a net loss occurs in the articular cartilages of patients with osteoarthritis and rheumatoid arthritis, leading to cartilage degeneration and loss of joint function [173]. In psoriasis there is increased excretion in urine of DS, which is correlated with the amount of diseased skin [179]. Diabetics exhibit increased urinary excretion of HS [19] which probably reflects enhanced degradation of basement membranes, which have a reduced GAG content in diabetes [163]. Tumour cells may utilize an extracellular endoglucuronidase to cleave basement membrane HS proteoglycans. B16 melanoma cells contain such an enzyme [143] and more metastatic sublines produce increased amounts [142].

Conclusions

Proteoglycans are now the focus of much research. It is becoming increasingly apparent that they play a multitude of key roles in the normal physiology of cells and tissues and that disturbances in their metabolism can produce a variety of pathological changes. In this brief review I have endeavoured to highlight the diversity of form and function and examine their synthesis and degradation. Inevitably this limits discussion to only a very small proportion of the literature. I do, however, hope that this overview will act as a stimulus to more research and a greater understanding of these remarkable molecules.

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